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Kohtala, Samuel

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MINIREVIEW

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Rapid-acting antidepressants and the regulation of TrkB neurotrophic signalling—Insights from ketamine, nitrous oxide, seizures and anaesthesia

Samuel Kohtala[1,2,3] | **Tomi Rantamäki**[2,3]

[1]Department of Psychiatry, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA

[2]Laboratory of Neurotherapeutics, Drug Research Program, Division of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland

[3]SleepWell Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Correspondence
Samuel Kohtala, Department of Psychiatry, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA.
Email: Samuel.kohtala@helsinki.fi

Funding information
Orionin Tutkimussäätiö; Sigrid Juséliuksen Säätiö

Abstract

Increased glutamatergic neurotransmission and synaptic plasticity in the prefrontal cortex have been associated with the rapid antidepressant effects of ketamine. Activation of BDNF (brain-derived neurotrophic factor) receptor TrkB is considered a key molecular event for antidepressant-induced functional and structural synaptic plasticity. Several mechanisms have been proposed to underlie ketamine's effects on TrkB, but much remains unclear. Notably, preliminary studies suggest that besides ketamine, nitrous oxide (N_2O) can rapidly alleviate depressive symptoms. We have shown nitrous oxide to evoke TrkB signalling preferentially after the acute pharmacological effects have dissipated (ie after receptor disengagement), when slow delta frequency electroencephalogram (EEG) activity is up-regulated. Our findings also demonstrate that various anaesthetics and sedatives activate TrkB signalling, further highlighting the complex mechanisms underlying TrkB activation. We hypothesize that rapid-acting antidepressants share the ability to regulate TrkB signalling during homeostatically evoked slow-wave activity and that this mechanism is important for sustained antidepressant effects. Our observations urge the examination of rapid and sustained antidepressant effects beyond conventional receptor pharmacology by focusing on brain physiology and temporally distributed signalling patterns spanning both wake and sleep. Potential implications of this approach for the improvement of current therapies and discovery of novel antidepressants are discussed.

KEYWORDS

electroencephalogram, energy metabolism, protein phosphorylation, rapid-acting antidepressant, sleep

1 | INTRODUCTION

Major depression is highly prevalent, debilitating and economically burdensome psychiatric disorder. Pharmacotherapy with conventional antidepressants (eg selective serotonin reuptake inhibitors) is the most commonly used treatment option, but a large proportion of patients do not receive sufficient benefit and remain treatment-resistant. The discovery of the rapid-acting antidepressant effects of the N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine, a

dissociative anaesthetic drug, has brought renewed interest towards the research and development of antidepressants with a more rapid onset of action.[1] The antidepressant effects of a single intravenous dose of subanaesthetic ketamine (0.1-0.5 mg/kg, *iv*) are typically observed already within a few hours, although in most cases the effects become more prominent the following day.[1-4] However, the antidepressant effects of ketamine are transient and commonly sustained for only up to a week.[5]

Two decades of intensive research have led to many important discoveries about ketamine's antidepressant effects, yet the precise mechanism through which ketamine exerts its therapeutic effects remains unclear.[4,6-9] Subanaesthetic dose ketamine is thought to preferentially block of NMDARs expressed in inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons.[9] By reducing GABAergic tone, ketamine disinhibits the activity of glutamatergic pyramidal neurons, leading to enhanced glutamate release and bursting. Increased glutamate activates post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). These, and other mechanisms induced by ketamine, have been proposed to ultimately converge on increased translation and release of brain-derived neurotrophic factor (BDNF), a key regulator of antidepressant actions[4] (Figure 1). BDNF and its receptor TrkB can regulate a myriad of downstream signalling effectors leading to increased transcription, translation and trafficking of the components involved in synaptic plasticity. Recent studies have also proposed that ketamine's antidepressant effects are mediated by its 2R,6R-hydroxynorketamine (HNK) metabolite,[10] or that ketamine and HNK directly bind to TrkB receptors and facilitate their responsiveness to BDNF.[11] Despite these findings, the dose and time-dependent effects of ketamine, or its metabolites, on TrkB phosphorylation and signalling in the adult brain have been only scarcely studied.

Ketamine has relatively short half-life, and its antidepressant effects greatly outlast acute receptor-level effects triggered by the drug.[9] Early clinical evidence indicates that nitrous oxide, a gaseous NMDAR antagonist that is eliminated (unchanged) even more rapidly, may also produce rapid and sustained antidepressant effects.[12] The emergence of these rapid yet sustained effects is difficult to explain through principles of conventional receptor pharmacology, which have been previously applied to the study of monoaminergic drugs. Moreover, some non-pharmacological treatments capable of inducing prominent changes on glutamatergic system and global brain activity, most notably sleep deprivation and treatments inducing transient seizures (eg electroconvulsive therapy (ECT)), also possess rapid antidepressant potential.[6,13,14] Therefore, the antidepressant effects of ketamine, and other rapid-acting treatments, may be connected to shared molecular and physiological adaptions in brain networks that

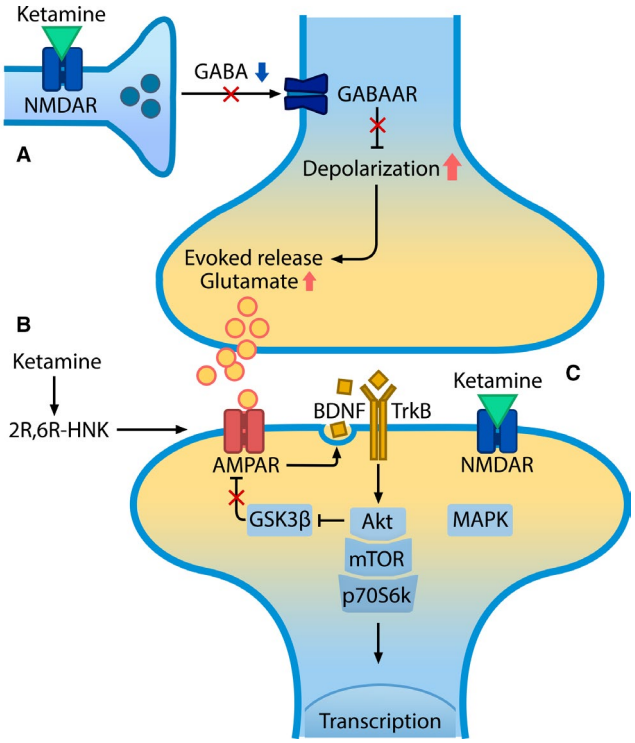

FIGURE 1 Some of the proposed mechanisms underlying subanaesthetic ketamine's effects on TrkB signalling. A, Ketamine blocks NMDARs on inhibitory GABAergic interneurons resulting in the disinhibition of glutamate release and the activation of post-synaptic AMPARs, which evoke BDNF synthesis and trafficking. Activation of TrkB leads to changes in downstream signalling including activation of p44/42-MAPK and mTor-p70S6k, and inhibition of GSK3β, which ultimately alter gene transcription (eg *Bdnf* and synaptic proteins). B, Ketamine metabolite 2R,6R-hydroxynorketamine (HNK) has been shown to regulate glutamate release in an NMDAR-independent manner. C, Blockade of post-synaptic NMDARs have been proposed to induce local translation of BDNF

underlie the pathophysiology of depression. However, the effects of nitrous oxide, sleep deprivation and seizures on TrkB signalling have not been systematically investigated. In this minireview, we overview our recent findings and efforts in this context, with an emphasis on the shared ability of rapid-acting antidepressants to increase neuronal excitation and synaptic potentiation in the cortex during their acute pharmacological or physiological effects. Moreover, we discuss the hypothesis that concomitant brain activity and associated molecular changes, which may emerge only after the excitatory effects of said treatments have waned off, may be important in understanding rapid antidepressant action. Finally, we summarize our observations related to the activation of TrkB signalling by nitrous oxide and seizures, which takes place preferentially after their acute effects on cortical excitation have subsided, giving way to a brain state dominated by slow delta frequency EEG activity resembling deep slow-wave sleep.[13] Subanaesthetic dose

ketamine also leads to the increases in slow-wave EEG activity after its acute excitatory effects have dissipated. We argue that understanding the complex neuronal responses to treatments like subanaesthetic dose ketamine—and their association with the neurobiology of sleep—could be an important piece of the puzzle towards a more comprehensive picture of fast-acting antidepressants and a starting point for the development of novel treatments against major depression.

2 | SHARED NEUROBIOLOGICAL BASIS FOR RAPID-ACTING ANTIDEPRESSANTS

2.1 | Cortical excitation

The molecular, functional and structural changes associated with subanaesthetic ketamine and other putative rapid-acting antidepressant treatments, such as nitrous oxide, sleep deprivation and electroconvulsive therapy, are strikingly similar despite clear physiological differences. For ketamine, the proposed mechanisms—more or less—converge on increased cortical excitation, often accompanied by increases in brain energy metabolism (reviewed in[4,6]). The induction of neuronal activity by subanaesthetic ketamine is thought to be mediated, at least in part, through the disinhibition of glutamate release.[9] By preferentially blocking NMDARs on inhibitory interneurons, ketamine may reduce the inhibition of excitatory pyramidal neurons resulting in increased glutamate release and bursting.[15,16] Anaesthetic doses, however, lead to more general inhibitory effects, presumably through widespread blockade of NMDARs also on principal neurons. While many studies have investigated the dose-dependent effects of ketamine, there is no clear clinical evidence for the antidepressant effects of ketamine being limited to a specific subanaesthetic dose.[4]

The subanaesthetic ketamine-induced glutamate release activates AMPARs and triggers post-synaptic signalling mechanisms, which have been proposed to include the rapid translation and release of BDNF and the activation of its receptor TrkB (Figure 1). Through the regulation of downstream mechanisms such as mitogen-activated protein kinase (MAPK) and the activation of the mammalian target of rapamycin (mTOR) and its effector ribosomal protein S6 kinase beta-1 (also known as p70S6K) and the inhibition of glycogen synthase kinase 3β (GSK3β), ketamine is thought to modulate the synthesis and trafficking of neurotrophic and synaptic proteins allowing anabolic effects on synaptic structure, function and number—at least in animal models of depression. Within hours of administration, ketamine appears to rapidly alter cortical neuronal activity and connectivity in both human beings and rodents,[6,17-19] which may be a consequence of synaptic potentiation. On a longer timescale, ketamine increases the formation of dendritic spines, especially in the medial prefrontal cortex of chronically stressed rodents, which has been suggested to be important for the sustained antidepressant effects.[17,20] These findings of restored connectivity and increased synaptic strength in animal models are mirrored by clinical observations in depressed patients receiving ketamine therapy.[6,19,21-23]

Electroconvulsive therapy and sleep deprivation (ie prolonged waking)—non-pharmacological treatments possessing rapid antidepressant potential—share the property of subanaesthetic ketamine to induce global cortical excitation, as well as many of the other functional and molecular features associated with ketamine.[6] In ECT, an induced alternating current forces groups of cortical neurons to fire simultaneously, ultimately resulting in the propagation and generalization of epileptiform activity. Seizures can also be provoked by pharmacological convulsants, such as flurothyl,[24] which either suppress inhibitory or activate excitatory receptors to elicit similar outcomes. The neuronal activity inducing effects and associated molecular alterations of convulsive therapies have been studied thoroughly in animals.[25,26] Most notably, flurothyl has been effectively used as treatments of depression in the past. Sleep deprivation also increases cortical excitation and extracellular glutamate levels. Notably, other experimental treatments with rapid and long-lasting antidepressant potential, such as scopolamine and psychedelic drugs, may also acutely increase cortical excitatory activity and glutamate release.[6] The effects of classic psychedelics such as psilocybin may, however, be more specific as their primary targets, the $5HT_{2A}$ receptors, are enriched in evolutionarily recent brain areas implicated in depression. Notably, we have recently shown that nitrous oxide also up-regulates markers of cortical excitability and induces MAPK signalling in the cortex of rodents.[13] Nitrous oxide has shown initial promise in treating depression, but larger clinical trials are still underway.[12]

The aforementioned studies establish a perspective suggesting that a shared feature for clinically effective rapid-acting antidepressants is not any particular receptor or a subcellular target, but a more fundamental change in cortical activity (eg increased glutamate bursting and cortical excitation), which leads to the activation of molecular pathways and synaptic function resulting in antidepressant effects through physiologically evoked changes in functional connectivity, synaptic strength and synapse number.[6] While it is tempting to connect these changes with mechanisms such as BDNF-TrkB signalling, the exact temporal gradients of these molecular changes have not been thoroughly investigated. However, as will be next discussed, studies with nitrous oxide

and flurothyl have given insights to the regulation of these signalling mechanisms.

2.2 | Rapid-acting antidepressants, slow electroencephalogram activity and TrkB signalling

The exceptional pharmacokinetics of nitrous oxide and flurothyl make it possible to better differentiate acute pharmacological effects emerging during receptor engagement from those emerging immediately thereafter[13] (Figure 2). To this end, we have conducted pharmaco-EEG studies and molecular analyses to show that during the ongoing blockade of NMDARs, that is during active gas flow and inhalation, nitrous oxide produces no regulation in the phosphorylation of TrkB, GSK3β and p70S6K.[13] The regulation of these pathways only became regulated gradually once the gas flow was suspended. This period following the cessation of nitrous oxide flow was characterized by increases in the EEG delta (~1-4 Hz) frequency power—a phenomenon also observed in human studies following nitrous oxide administration.[27] Similarly, these signalling pathways remained unregulated in samples collected immediately following a flurothyl-induced seizure (Rosenholm et al, unpublished), while strong phosphorylation of TrkB, GSK3β and p70S6K was present in brain samples collected 15 minutes later during the post-ictal period,[13] another brain state which demonstrates prominent slow EEG activity. These studies suggest that the regulation of molecular pathways deemed important for antidepressant-like responses, such as activation of TrkB, to occur after the primary pharmacological effects of the treatments have subsided (Figure 2). Furthermore, these results may suggest that events related to synaptic plasticity and protein synthesis are differentially regulated during acute excitation evoked by the treatments versus the following adaptive state. However, studies with cellular resolution will be required to specifically localize the molecular changes.

The coinciding nature of slow EEG activity and TrkB signalling is also demonstrated by sedative drugs, which directly increase inhibition in the brain by different mechanisms.[13] GABAergic volatile anaesthetics sevoflurane and isoflurane produce prominent TrkB phosphorylation.[28] The effect of isoflurane on TrkB signalling is dose-dependent and most obvious changes are observed at dosing leading into deep anaesthesia.[29] Moreover, the α_2 noradrenergic agonist medetomidine—another hypnotic/sedative drug—readily activates TrkB receptors and increases slow-wave sleep like EEG activity.[13] Surprisingly, we have also found high and sedative doses of ketamine, but not low subanaesthetic, to acutely induce TrkB signalling, again accompanied by increased slow EEG activity.[14] Notably, the ability of sedative doses of ketamine to increase TrkB signalling acutely appear independent of its HNK metabolite.[14] However, to date, no thorough characterization which would feature multiple time-points of drug delivery has been made of the time- and dose-dependent effects of ketamine or other putative rapid-acting antidepressants on these pathways. Most importantly, while TrkB signalling and associated mechanisms have been connected with rapid antidepressant effects, it remains unlikely—and against clinical knowledge and experience—that purely sedative drugs would work as antidepressants. Here, we speculate that while the sedative state may effectively trigger molecular pathways important

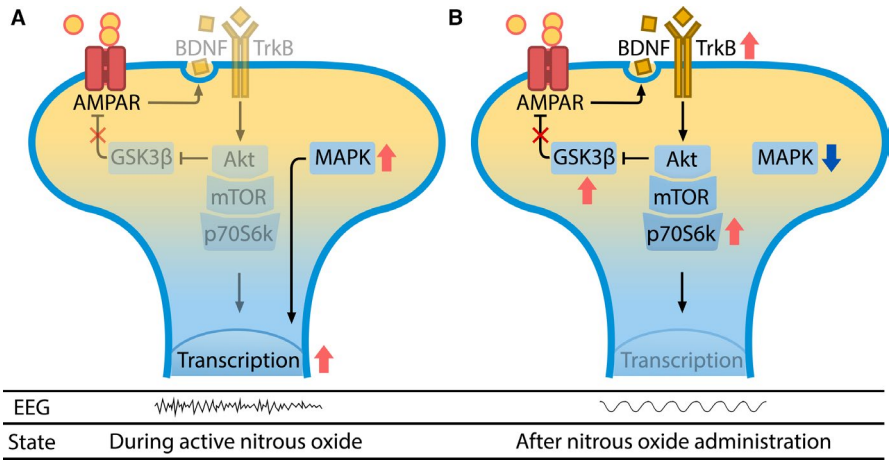

FIGURE 2 Molecular mechanisms regulated during and after nitrous oxide treatment in mice. A, During the acute effects of nitrous oxide EEG remains active, the phosphorylation of p44/42-MAPK$^{T202/Y204}$ is up-regulated and the transcription of immediate-early genes (eg *Bdnf*) is increased, while phosphorylation of TrkB^{Y816}, p70S6k$^{T421/S424}$ and the inhibitory Ser9 residue of GSK3β, remain unchanged. B, After nitrous oxide administration has ceased and the gas is eliminated from the brain, slow EEG activity becomes up-regulated along with increased TrkB^{Y816}, p70S6k$^{T421/S424}$ and GSK3β^{S9} phosphorylation, while p44/42-MAPK$^{T202/Y204}$ phosphorylation is decreased. Red arrows pointing upwards depict increased phosphorylation and blue arrows pointing downwards depict reduced phosphorylation

for antidepressant effects, activation of these pathways may only be relevant in the context of the preceding treatment-induced cortical activation (ie a physiological driver of plasticity). This idea brings us to review this phenomenon from the perspective of sleep.

2.3 | Sleep and rapid-acting antidepressants

During physiological non-rapid eye movement (NREM) sleep, slow and synchronized cortical EEG activity becomes pronouncedly up-regulated during bouts of slow-wave sleep.[8] Slow-wave sleep is generally thought to be important for facilitating or maintaining synaptic homeostasis, learning and memory. Indeed, from the perspective of the brain, the 24-hour circadian cycle represents the interplay of a state of increased activity, which takes place throughout wake and is thought to induce synaptic potentiation for learning and memory, and reduced activity represented by the disconnection of the brain from the external environment during sleep. According to the influential synaptic homeostasis hypothesis (SHY),[30] sleep is "the price the brain pays for plasticity." Indeed, numerous studies have shown the connection of cortical activation, be it sleep deprivation, a motor coordination task or even local activation of brain networks by using transcranial magnetic stimulation, to the increased emergence of slow-wave activity (SWA) during subsequent slow-wave sleep (SWS). Neuronal utilization during wake, as such, has been shown to be sufficient to up-regulate BDNF levels and induce rebound SWA in rodents.[31] Within this context, we believe subanaesthetic ketamine, and related treatments, may rapidly incite cortical microcircuits resulting in increased synaptic potentiation and strength.[6,8] This is reflected in the increased amount of SWA which can be measured during subsequent sleep.

The SHY proposes that SWS may have an important function in maintaining functional synaptic homeostasis.[30] A process entailing the renormalization of synaptic strength has been suggested to take place throughout deep sleep, where wake-up regulated levels of synaptic potentiation are returned to preceding levels. Here, synapses that were most active and potentiated during the day may preferentially remain protected from the renormalization and thus allow for relative changes in synaptic strength to be maintained. While the underlying mechanisms remain speculative, the main principle is supported by ultrastructural and molecular studies, which show both the reduction of synapse size and synaptic AMPARs during sleep.[32,33]

The potential association of ketamine's effects with sleep homeostasis is strengthened by clinical findings, where ketamine was found to increase total sleep time, SWS and REM sleep in treatment-resistant depressed patients.[34,35] Most importantly, the increases in the amount of SWA correlated with clinical improvement (ie antidepressant effects). These preliminary studies represent just a small fraction of the emerging studies connecting both sleep and circadian mechanisms to ketamine's antidepressant effects.[8] With that being said, the study of ketamine in this context may prove to be particularly fruitful for understanding its complex interaction with neurobiological mechanisms of sleep. Our recent effort in integrating some of the ideas of SHY to the study of rapid-acting antidepressants is known as the hypothesis of encoding, consolidation and renormalization in depression (ENCORE-D),[6] a framework which discusses these themes beyond the scope of this review.

3 | POTENTIAL SCIENTIFIC AND THERAPEUTIC IMPLICATIONS

As overviewed in the previous chapters, the effects of rapid-acting antidepressants can be divided into different temporal phases based on the emerging electrophysiological, molecular and functional signatures. We hypothesize that these phases constitute mechanisms that work in conjunction to achieve alterations in neural network function which ultimately become visible as the amelioration of depressive symptoms.[6] Agents that facilitate SWA directly without the preceding cortical excitation are likely not to function as rapid-acting antidepressants, despite the regulation of some of the molecular cascades implicated in synaptic plasticity and ketamine's antidepressant effects, such as activation of TrkB and inhibition of GSK3β. However, these mechanisms may be related to the emergence of antidepressant effects in the context of relevant neural activity and processes that may occur following cortical excitation and throughout sleep.[6] It is important to highlight the notion that most, if not all, of the neurobiological mechanisms associated with ketamine's antidepressant effects are interconnected with physiological circadian rhythmicity and/or the sleep-wake cycle[8] —a field of study which requires further attention. We will next discuss some of the potential scientific and therapeutic implications of the proposed mechanistic basis of ketamine and related rapid-acting antidepressants.

3.1 | Pharmacokinetics

One of the striking differences between ketamine and traditional antidepressant drugs is their pharmacokinetics. Ketamine is rapidly metabolized and is pharmacologically active for only a few hours (in rodents much less)—yet it produces a rapid amelioration of depressive symptoms that sustain long after the drug has been eliminated from the body. Whereas traditional antidepressants are administered

daily to eventually achieve steady-state concentrations, ketamine treatment focuses on giving a short infusion or a bolus dose. The antidepressant effects of ketamine begin to emerge immediately during the drug delivery and typically reach the peak effect after a night of sleep. What makes ketamine and agents such as nitrous oxide special maybe their relatively short duration of action, which is enough to induce cortical activity but also short enough not to perturb neuronal homeostasis (c.f. relapse after sleep deprivation, see Chapter 3.3). Here, drugs like MK-801, phencyclidine (PCP) and memantine differ both in their actions towards NMDARs but also in their pharmacokinetics. For example, memantine, which has not demonstrated clear antidepressant effects in clinical trials,[36,37] has a half-life of several days in human beings. The rapid properties of ketamine may explain the unique homeostatic adaptations it can trigger, and they encourage—somewhat counterintuitively—the search of novel rapid-acting antidepressant drugs with even shorter duration of pharmacological action. Similar potential may be held by psychedelic drugs with a rapid action, such as dimethyltryptamine (DMT).[38]

3.2 | Dose and dosing matters

Ketamine is a good example of a drug whose effects greatly vary depending on the dose. Low subanaesthetic doses increase cortical excitability and glutamatergic neurotransmission, whereas high anaesthetic doses suppress neural activity.[15,39,40] As previously explained, low and high doses follow different dynamics in activating various molecular pathways implicated in antidepressant responses. Surprisingly, it remains unknown whether high doses of ketamine also possess antidepressant efficacy. High doses may also have a window of pharmacological action when they primarily induce excitation, for example when majority of the dose has been metabolized and the patient is again becoming responsive. Indeed, many anaesthetics display post-anaesthesia reactions known as emergence phenomena, where patients may show agitation, confusion and hallucinations.[41] Such reactions are also relatively common with volatile anaesthetics, which could similarly facilitate paradoxical excitation of the cortex during low drug concentrations.[42] To our knowledge, no clinical trials have addressed whether subanaesthetic doses of volatile anaesthetics would possess antidepressant actions, although an interesting recent case report with sevoflurane indicate this.[43] Notably, it may be that there is no optimal dosage that can be generalized to apply to every patient. Volatile and gaseous anaesthetics, however, can be easily titrated almost in real time to a concentration or dosing that is most beneficial for the treatment, for example from the perspective of inducing optimal cortical activation and subsequent facilitation of slow-wave activity.

3.3 | Slow-wave sleep and consolidation of antidepressant effects?

The study rapid-acting antidepressants in the context of sleep may be one of the key aspects towards understanding the underlying neurobiological mechanisms. In this mini-review, we have focused on hypotheses revolving around slow-wave sleep, but many other aspects and stages of sleep may turn out to be equally important. With that being said, slow-wave sleep presents an intriguing candidate for future studies to investigate in the context of rapid-acting antidepressant treatments. Experiments where slow-wave sleep is either disrupted or enhanced following ketamine treatment may provide important clues to the neurobiological significance of sleep in general, as well as its role in the consolidation of antidepressant effects.[6,8] In this context, it is important to note that sleep deprivation effectively and rapidly alleviates depression, but the depressive symptoms often re-emerge after a subsequent sleep period or even a short nap. It is tempting to speculate that the fragility of the antidepressant effects of sleep deprivation is associated with disruption of sleep physiology and thereby mechanisms allowing sustained antidepressant effects. Altogether, the disregard for sleep in both clinical and basic research may have more generally contributed to the soaring numbers of translational failures and hindered our ability to understand the core of ketamine's antidepressant action.[8,44]

3.4 | Biomarker predicting rapid antidepressant efficacy

The post-ictal emergence of slow-wave EEG activity following ECT has been proposed to predict its efficacy and onset of antidepressant effects many decades ago[45,46]—long before the emergence of molecular signalling perspectives associated with antidepressant actions. Perhaps for this reason, the potential neurobiological significance of the EEG suppression has remained poorly studied in experimental models. Our observations associate slow-wave EEG activity with the activation of the key molecular pathways implicated in rapid antidepressant effects and suggest there may be more to uncover in this association.[6] Clinical studies demonstrating that subanaesthetic ketamine (and sleep deprivation) trigger homeostatic increases in slow-wave EEG activity further strengthens the association between slow-wave EEG, clinical responses and the neurobiology of sleep.

Studies have reported several EEG (or MEG (magnetoencephalogram)) findings to coincide with the emergence of ketamine's antidepressant effects. In psychiatric ECT, EEG is used to monitor seizure quality and the post-ictal emergence of slow EEG activity. Similarly, EEG could have potential in monitoring the cortical activation, and putative subsequent slowing, induced by ketamine and other potential rapid-acting antidepressant treatments. Our studies in rodents associate the emergence of slow EEG activity with the activation of molecular pathways important for synaptic plasticity, which suggests that similar changes may also take place in the human brain under similar physiological conditions. However, further studies precisely characterizing the patterns of EEG activity and associated molecular changes are required. Moreover, understanding other physiological changes associated with the emergence of increased SWA or up-regulation of delta EEG power, such as changes in brain metabolism and glymphatic flow (that is increased during deep sleep and anaesthesia), may ultimately provide key information to understand the neurobiological significance of these phenomena.

3.5 | Circadian time of administration

The mechanisms overviewed in this review, such as the ability of rapid-acting antidepressants to provoke cortical excitation and the subsequent emergence of slow EEG activity, suggest that the baseline brain state (ie level of excitability) of the underlying neural networks may ultimately determine outcomes of a treatment. Both homeostatic[47] and circadian factors[48] influence excitability, thus promoting the idea that the circadian time of drug or treatment administration may be relevant for the emergence of the therapeutic effects. For example, treatments administered early in the morning could produce different outcomes compared to those late in the evening.[8] To this date, no studies have thoroughly addressed this question. The question is also of significant interest in terms of basic animal research, since most commonly used laboratory rodents are nocturnal (ie night-active).[44] Although the contrast in their activity throughout vigilance states is not as clear as in human beings, there is a clear preference for sleep and rest during the light period, when most experiments (eg drug treatments, behavioural analyses and collection of samples for biochemical analyses) are conducted. Thus, neglecting this issue may contribute to the problems in translating findings from basic research to the clinic.[44]

4 | CONCLUSIONS

Activation of the BDNF receptor TrkB and its downstream signalling has been tightly connected with ketamine's antidepressant effects. Despite an ever-increasing number of proposed mechanisms underlying ketamine-induced TrkB signalling and prospective targets and putative antidepressant drugs—mostly found using traditional depression models—few drugs have advanced further in the pipeline and none have come close to surpassing ketamine. We have taken another strategy by aiming to understand the effects of rapid-acting antidepressants by comparing the molecular and physiological effects of drugs and treatments proven effective or shown promise in clinical studies including sleep deprivation, seizures and nitrous oxide. Our observations indicate that these mechanistically diverse treatments share the ability of triggering prominent activation of cortical networks. Importantly, phosphorylation of TrkB and activation of its downstream signalling is largely unchanged during this initial excitation phase produced by the treatments and become only gradually regulated after the acute pharmacological/physiological effects have dissipated. Notably, the activation of TrkB signalling appears to coincide with several characteristic features of deep sleep, most notably the facilitation of slow-wave EEG activity. While the mechanisms involved in the activation of these molecular signalling events remain unknown, we hypothesize that treatments possessing rapid antidepressant potential share the ability to up-regulate TrkB signalling during homeostatically evoked slow-wave sleep, and that this mechanism may be associated with regulation of synaptic plasticity during sleep. Here, future studies aimed at dissecting the temporal and spatial characteristics of rapid-acting antidepressants effects throughout wake and sleep are warranted.

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CONFLICT OF INTEREST

TR and SK are listed as co-inventors on a patent application wherein new tools enabling the development of rapid-acting antidepressants and the efficacy monitors thereof are disclosed based on the basic principles of ENCORE-D. TR and SK have assigned their patent rights to the University of Helsinki but will share a percentage of any royalties that may be received by the University of Helsinki.

ORCID

Samuel Kohtala https://orcid.org/0000-0001-9249-085X

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